

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 December 2002 (12.12.2002)

PCT

(10) International Publication Number
WO 02/098926 A2

(51) International Patent Classification⁷: C08F 8/00

(21) International Application Number: PCT/EP02/06433

(22) International Filing Date: 3 June 2002 (03.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/297,714 4 June 2001 (04.06.2001) US

(71) Applicant (for all designated States except US): UNIVER-
SITE DE LIEGE [BE/BE]; Interface Entreprises Univer-
sité, Antheunis Nicole, Quai Van Beneden, 25, B-4020
Liege (BE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BERTRAND**,
Olivier [BE/CA]; Chemin St-Louis, 2590, Sainte-Foy,
Québec G1W1N2 (CA). **JEROME**, Robert [BE/BE]; Rue
Alexandre Beaupain, 4, B-4845 SART-JALHAY (BE).
GAUTIER, Sandrine [BE/BE]; rue Bois-l'Evêque, 132,
B-4000 Liege (BE). **MAQUET**, Véronique [BE/BE];
Hameau de Crenwick, 19, B-4257 Berloz (BE). **DE-
TREMBLEUR**, Christophe [BE/DE]; Wolfskaul, 5,
51061 Köln (DE). **JEROME**, Christine [BE/BE]; rue
de la Jacinthe, 10, B-4102 Ougree (BE). **VOCCIA**,
Samuel [BE/BE]; rue Saint Michel, 46, B-4000 Liege
(BE). **CLAES**, Michael [BE/BE]; Rue Ernest Malvoz,
49, B-4020 Liege (BE). **LOU**, Xudong [CN/BE]; Place
général Leman, 41, B-4000 Liege (BE). **LABAYE**,
David-Emmanuel [BE/BE]; Rue Hubert Désamuré, 29,
B-4000 Liege (BE).

(74) Common Representative: UNIVERSITE DE LIEGE;
Interface Entreprises Université, Antheunis Nicole, Quai
Van Beneden, 25, B-4020 Liege (BE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES,
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,
MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG,
UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS,
MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI,
CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for all designations

Published:

- without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR DEPOSITING STRONG ADHEREND POLYMER COATING ONTO AN ELECTRICALLY CON-
DUCTIVE SURFACE

(57) Abstract: Process for depositing by electrografting a strong adherent polymer coating onto an electrically conductive surface comprising an electrochemical grafting at the surface of an active monomer for forming a primer coating P onto said surface and having as general formula: X0 (meth)acrylate wherein X is either part of a preformed polymer or is an intermediate agent for polyad-
dition reaction or is an anchoring group for attachment of a molecule having at least one complementary reactive group. Such process allows formation of new primer by one-step electro-grafting of a reactive polymer called macromonomer. Such process also allows further modification of an initial electrografted polymer (called primer coating) to increase the coating thickness by the so-called grafting-from technique i.e. polymerization of a second monomer or to introduce other types of polymers (also called top coating) via covalent attachment between the primer and the top coating through the X ester group by the so-called grafting onto technique. Such process also allows to graft onto the primer coating compounds like functional polymer, peptide, protein, oligonucleotide, dyes, drugs, anti-bacterial compounds.

WO 02/098926 A2

PROCESS FOR DEPOSITING STRONG ADHERENT POLYMER COATING ONTO AN ELECTRICALLY CONDUCTIVE SURFACE.

5 The invention concerns a process for depositing by electro-grafting a polymer coating onto an electrically conductive surface.

10 It is well known that the surface of a variety of organic and inorganic substrates is coated by synthetic polymers in order to impart them specific properties (e.g. adhesion, hydrophilicity or hydrophobicity, low friction, resistance to environmental attack, biocompatibility, etc.). These coated surfaces are an extreme example of composites, comprising constitutive components having a layered structure. In such a field, a major problem to be solved is the usually weak and short-term adhesion between completely different substrates, 15 such as metal, glass, carbon and organic polymer. Covalent bonding at the interface is often considered as a target to be reached. In this respect, electropolymerisation of acrylates or methacrylates has proved to be a powerful tool to deposit polymers strongly adhering to electrically conducting substrates. Delamar and al in Carbon 1997,35,801 have demonstrated that electroreduction 20 of these acrylates or methacrylates monomers at an appropriate potential, leads to a rapid formation of a homogeneous polymer coating on the cathode whatever its shape (plate, fiber) and nature (metals alloys, carbon, Indium Tin Oxideglass,...).

25 However, several problems limit the use of electropolymerization to practical applications: film thickness is small (<100 nm) due to a fast termination of grafted polymer brushes, and the monomers which can be electrografted are restricted to one (although large) family of activated vinylic monomers e.g. acrylate, cyano, cyano-acrylate, pyridine... compounds. As a rule, 30 the carbon-carbon double bond must be activated by an electron withdrawing substituent for the monomer to be reactive at the cathode and to be adsorbed on it preferably to the solvent. Additionally, any function, such as alcohol, protic

amine and carboxylic acid, which are reduced at a less cathodic potential than the monomer cannot be tolerated.

5 These serious restrictions considerably shorten the list of eligible monomers, hence the list of strongly adherent coatings that can be achieved on conductive surface via electro-grafting, and hence the usefulness of electrografted coatings in practical applications.

10 In particular when the surface of the substrate belongs to metallic prostheses such as for example structure-support implants, as for example bones plates, bone screws, femoral heads, stent, dental implants problems of biostability and biocompatibility are important.

15 For example, when applied to stent which serves as scaffolding to the vessel wall after percutaneous vessel enlargement, a well known limitation to existing stents is their limited hemo and tissue-compatibility. After stent implantation, inflammatory response does occur which in turn might promote local thrombosis activation and/or smooth muscle cells and myofibroblasts migration and proliferation. Stent implantation might also delay normal endothelial regeneration after vessel injury. This might ultimately results in further lumen obstruction impeding normal blood flow to the heart. This process
20 has been called restenosis. Therefore, there is a need to develop more biocompatible stent possibly capable to release bioactive compounds to modify tissue reactions to metallic stent implantation. Previous attempts to coat metallic stents with polymers have failed in part due to inadequate bonding between the polymer matrix and the stent surface. Indeed, with previous coating techniques, stent deployment and/or sterilization created breaks, fissures in the polymers or detachment of the coating from the stent surface. In addition, preliminary results on the release of drugs inhibiting restenosis, such as sirolimus or taxol, seem to indicate that adequate global average release rates amount to a 100 to a few
25 100's of micrograms of drug over a few months. Alternatively, it is known that the release kinetics remains controlled by the encapsulating polymer as far as the
30 drug content in the polymer matrix remains lower than about 10 to 20%. This

also indicates the need for a better adhesion and an increase thickness of drug releasing polymer layers for this type of application.

5 A certain number of applications require barrier coatings, capable either to prevent corrosion of the underlying metal (cars, medical devices such as stents, dental implants, guidewires...etc), or to disfavor adsorption of biological molecules onto the surface when put into contact with biological fluids and/or implanted. Such problems is encountered e.g. in biochips (non specific adsorption, which affects signal-to-noise detection ratios), and in general on the active zone of physical or chemical sensors (e.g. adsorption of proteins on
10 pressure sensors, glucose sensors...etc), as well as for packaging applications on micro-systems (should they be implanted or not). In these cases, polymers stemming from electro-graftable monomers often fail to provide a good a durable protective coating, either because of their structure, or because of their low thickness, or both. Additionally, very low thickness is also synonymous with a
15 high sensitivity to scratching : the thickness of traditional electro-grafted polymers is by far lower than the rugosity of the surface of most objects, which thus pit the electro-grafted layer as soon as they are put into contact with it, ruining its tentative protective characteristics.

Intermediate thicknesses (i.e. of the order of a micron or of a few
20 microns) are also desirable to get insulating layers capable of resisting mechanical contact, insertion/desinsertion or friction cycles, such as in connectic (computers, mobile phones...etc), micromechanics and electrical devices in general in which a metallic part is put into contact with the polymer coating. As a rule, the rugosity of the metallic part is higher than one micrometer (since
25 getting to lower rugosities requies specific treatments), and durable coatings must therefore be thicker than one micron.

A clear need thus emerges for strongly adhering polymer coatings on conductive surfaces about a micrometer or even a few micrometers thick.

30 One definite advantage of the electro-grafting is the capability to force the formation of interface - presumably covalent - carbon/metal bonds, with high grafting ratios : parameters of the electrochemical protocol can be defined to favour the formation of grafted polymer brushes, for which controlling the

thickness amounts to controlling the molecular mass of the grafted chains. As outlined above, the growth of polymer chains is probably hindered and stopped at an early stage, leading to pretty short chains, or in any case to chains the length of which cannot be easily controlled on the basis of traditional macromolecular strategies. A first direction towards obtaining thicker polymer films is thus to be able to achieve the grafting of polymer chains of high molecular mass.

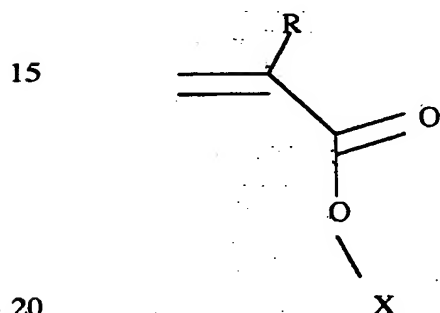
Besides the physical characteristics of the polymer layer (thickness, compacity...etc), the very chemical nature of the polymer layer to be grafted is also important.

Microsystems designed for biomedical applications are packaged by biocompatible coatings of polymeric nature, such as e.g. parylene (which is deposited by Chemical Vapor Deposition, CVD) or PDMS (Poly DiMethyl Siloxane), which enable a correct biocompatibility as well as an interesting chemical resistance. High performance lubrication capabilities – i.e. low friction coefficients – are offered by perfluoro polyether layers, e.g. on connectors or mechanical parts. None of these polymers can be obtained as the result of electro-initiated propagation reaction. Identically, one cannot straightforwardly get e.g. electro-grafted poly-imides, poly-amides (which are good candidates in microelectronics for highly insulating polymers as they afford low k dielectric layers), and in general polymers obtained by polycondensation reactions. Rather than thinking of which vinylic polymer may provide properties identical to these materials, the need is great to provide a process thanks to which these polymers may nevertheless be grafted onto conducting surfaces.

Due to the relatively short list of functional groups an activated vinylic monomer can bear to be eligible for electrografting, electro-grafted polymers offer a restricted catalog of functionalities to fix additional layers by conventional chemical methods, such as those used e.g. in the solid support synthesis of peptides, the fixing of oligonucleotides (DNA chips) or proteins (protein chips). Thus, even in the restricted domain of activated vinylic monomers, a need remains to enlarge the list of molecules capable of providing reactive coatings by electro-grafting.

We have now found a process for depositing by electro-grafting new
5 types of strong adherent polymer coating onto an electrically conductive surface,
which solve the problems mentioned above.

Accordingly, the present invention provides a process for depositing by
electro-grafting a strong adherent polymer coating on an electrically conductive
10 surface comprising an electrochemical grafting at the surface of an active
monomer for forming a primer coating P onto said surface and having as general
formula:



wherein R represents hydrogen or methyl
and the monomer comprises an X group
which is part of a preformed polymer or
25 is an intermediate agent for polyaddition reaction or
is an anchoring group for attachment of a molecule having at least one
complementary reactive group.

When X is part of a preformed polymer, the monomer becomes a
30 macromonomer bearing at least one activated vinylic pendant group, e.g. an
acrylic or methacrylic function. Such approach allows formation of new primer
by one-step electro-grafting of a reactive polymer called macromonomer.

Such process also allows further modification of an initial electrografted polymer coating (called primer coating P) to increase the coating thickness by the so-called grafting-from technique i.e. polymerization of a second monomer (called M in fig2) or to introduce other types of polymers (also called top coating) via covalent attachment between the primer and the top coating through the X ester group by the so-called grafting-onto technique.

Such process also allows to graft onto the primer coating compounds like functional polymer, peptide, protein, oligonucleotide, dyes, drugs, , anti-bacterian compounds.

By electrografting, and as illustrated in fig 1, wherein A is a solvent and B a conducting salt, one means the electrografting of the monomer on the conductive surface S to form a primer electrografted polymer coating P. In such electrochemical process, the monomer is electrochemically polymerized and simultaneously the so-formed polymer is electrografted onto S.

By macromonomer, one means, a preformed polymer bearing at least one acrylic or methacrylic function as illustrated in Fig 3.

By grafting-from, and as illustrated in fig 2(I), one means, initiation of the polymerization of a second monomer M from the group X of the grafted monomer which serves as grafted macroinitiator or transfer agent.

By grafting onto, and as illustrated in fig 2(II), one means bonding of O-Y, a preformed polymer or any reactive molecule or macromolecule onto the conductive surface, through the Y complementary reactive group with the X group of the monomer.

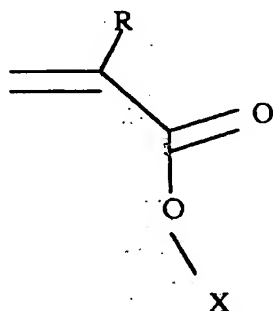
By intermediate agent one means an initiator or a transfert agent for a polyaddition reaction.

The conducting surface according to the invention is for example steel, stainless steel, Inox316L, tantalum, titanium, nitinol, carbon, ITO glass, transition metal (Fe, Ni, Cu, Au, Ag,...), metal doped polymer. .

The electrochemical grafting at the surface is performed under well known conditions from a solution of the monomer in an aprotic solvent A containing a conducting salt B . The monomer solution is subjected to electrolysis so as to create a reaction for example a cathodic reaction wherein the conductive surface to be coated is used as cathode at a potential situated in the range of the electron transfer between the conductive surface and the monomer of a value equal or near the value corresponding to an inhibition peak of the cathodic reaction of the monomer, but less negative than the second reduction peak corresponding to the polymerization in solution and degrafting of the polymer coating

A first approach to solve the problems mentioned above is to combine the electro-grafting technique with a polymerization reaction.

In its first aspect, the present invention provides a process for depositing by electro-grafting a polymer coating on an electrically conductive surface comprising an electrochemical grafting at the surface of an active monomer for forming a primer coating P onto said surface and having as general formula:



wherein R represents hydrogen or a methyl and the X group is an intermediate agent for polyaddition reaction.

The monomer is bearing an intermediate agent of polymerisation in the ester group X and is electrografted onto the solid surface.

5 The intermediate agent may be an initiator for ring opening polymerization (ROP), for polymerization via nitroxyde radicals (NMP), for atom transfer polymerization (ATRP) or a transfert agent for polymerization via reversible-addition-fragmentation (RAFT)

10 This type of approach is particularly interesting as it allows a global covalent grafting of a variety of polymers onto conductive surfaces which is much larger than the restricted list of polymers whose monomers is strictly eligible for electro-grafting. The later list is the one dictated by the
15 aforementioned constraints of cathodic electro-grafting, namely the absence of labile protons, and the activation of the vinylic double bond by electron-withdrawing groups. For example, this new type of approach allows coatings of
20 polymers other than polyacrylates or polymethacrylates. Such new approach allows coatings of polymers such as for example polystyrene or polyhydroxyethylacrylate to be deposited on the conducting substrates with a strong adhesion and an increased and tunable thickness.

 The polyaddition according to the invention may be controlled or not. It may be a ring opening polymerization (ROP)[as described by P; Dubois et al. in
25 Makromol. Chem., Macromol. Symp. 42/43, 1991, 103], a radical polymerization such as for example atom transfer polymerization (ATRP)[as described in Matyjaszewski, Curr. Org. Chem., 2002,6, 67], polymerization via nitroxyde radicals (NMP) [as described in Chem. Rev., 2001, 101, 3661],
30 polymerization via reversible-addition-fragmentation (RAFT) [as described by Moad et al., in polym. Int., 49, 993, 2000] or a combination of two different controlled polyaddition such as ATRP and ROP.

The Ring opening polymerization (ROP) may be applied to lactones and lactides such as (ϵ -caprolactone), and functional caprolactones such as γ -bromo- ϵ -caprolactone, or lactide such as D,L-Lactide...or any other polymerizable cyclic monomer such as trimethylene carbonate, cyclic anhydride, glycolide....

5

In ROP, X may be a metal carboxylate such as aluminium carboxylate or a metal alkoxide such as aluminium alkoxide, stannous alkoxide, titanium alkoxide, magnesium alkoxide or zinc alkoxide.

Monomers used as precursor for ROP process are for example trimethylsilylhydroxy(meth)acrylate, glycidyl (meth)acrylate, ethyl acrylate
ROP experimental conditions are well known by the man skilled in the art.

10

The radical polymerization may be applied for the obtention of vinyl polymer of a wide range and predetermined molecular weight.

15

Examples of radical polymerization are ATRP, NMP, RAFT

20

In NMP, an alkoxyamine is used as initiator and mediator: A C-O bond of the alkoxyamine is thermally homolytically cleaved into two free radicals: a carbon centered radical, to initiate the polymerization and a nitroxide radical to regulate the radical polymerization. The cleavage of the C-O bond occurs by heating at a temperature between 40°C and 160°C, preferably 110 °C.

25

In ATRP, X may be a haloalkane, haloketone, haloester, halonitrile, haloalkylbenzene or sulfonyl chloride or any other function able to initiate atom transfer radical polymerization. For this process, an additional metallic complex has to be added with the monomer to catalyze the polymerization. The metal of such catalyst has to be chosen to be compatible with the surface. On easily oxidizable surfaces like iron, a commonly used copper catalyst has to be replaced by a more stable ruthenium based catalyst.

30

The controlled polymerization via reversible-addition-fragmentation (RAFT) may be applied to obtain vinyl polymer as described by Lee and al in

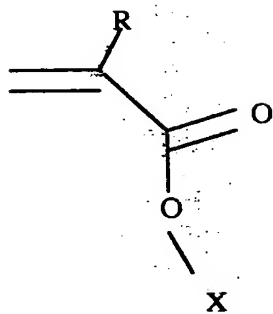
WO9801478 A1. In RAFT, X may be for example a dithioester, a dithiocarbamate, a trithiocarbonates or any other function able to control reversible-addition-fragmentation polymerization.

5 All polyaddition are performed under general conditions well known by the man skilled in the art.

A combination of the electro-grafting technique with a polymerization reaction as mentioned in the first aspect of the present invention allows a controllable
10 increase in the thickness of the coating at the surface and a better adherence of the polymer coating.

A second approach to solve the above problems is to use a macromonomer instead of a monomer.

15 In its second aspect, the present invention provides a process for depositing by electro-grafting a polymer coating on an electrically conductive surface comprising an electrochemical grafting at the surface of an active monomer for forming a primer coating onto said surface and having as general
20 formula:



wherein R represents hydrogen or methyl
and X is part of a preformed polymer.

In such approach, the monomer becomes a macromonomer bearing at least one acrylic or methacrylic function to be electrografted on the surface S as illustrated in figure 3.

5 The preformed polymer may be obtained by any type of polymerization technique such as by a controlled/living polymerization or not. The preformed polymer may be obtained for example by a polyaddition process with anionic, cationic, coordinative or radical initiation or by a polycondensation process.

10 The macromonomer may be an α - or an α -, ω -acrylic or methacrylic substituted polymer, a randomly acrylic or methacrylic functionalized copolymer, a diblock copolymer with one block bearing the acrylic or methacrylic groups, or any kind of macromolecular architecture (like stars, graft, tapered copolymers) which comprise active acrylic or methacrylic groups.

15 Fig 3 illustrates different examples of macromonomers.

Macromonomer (1) is a polymer with pendent acrylic or methacrylic groups, Macromonomer (2) is a α functionalized polymer and (3) is an α - ω fonctionnalized polymer.

20 The macromonomer has to be compatible with the electrode polarization, so that no other electroactive functions in the range of electrografting potential, except the acrylic or methacrylic groups, is present on the macromolecular architecture. For instance, no unprotected alcohol, no carboxylic acid, no amine, no bromide

25 should be present along the polymeric chain.

The macromonomer has also to be soluble in the electrochemical bath i.e. in polar solvents like dimethylformamide, dimethylsulfoxide, pyridine, acetonitrile, hexamethylphosphoramide,...

30 The process of electro-grafting with a macromonomer as mentioned in the second aspect of the present invention considerably broadens the list of

organic polymer coatings which may be obtained straightforwardly by electro-grafting, enabling a chemical engineering of the coating at the monomer level. It also allows for a better adhesion of the polymer coating at the surface.

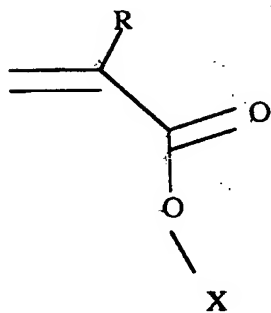
5

A third approach to solve the above problems is to combine electro-grafting with a grafting onto technique.

10

In its third aspect, the present invention provides a process for depositing by electro-grafting a polymeric coating on an electrically conductive surface comprising an electrochemical grafting at the surface of an active monomer for forming a primer coatingP onto said surface and having as general formula:

15



20

25

wherein R represents hydrogen or methyl
and X is an anchoring group for attachment of a molecule having at least one complementary reactive group.

30

In such approach, one have an X activated ester function towards nucleophilic compounds.

X may be for example a succinimidyl group particularly reactive towards amines. It may also be an epoxy, a vinyl, an allyl, an aryl, a chloride group or a combination of them.

- 5 Electro-grafting of such monomer provides a surface modified with a thin organic primer P suitable for further "grafting onto" process of a very wide range of molecules or macromolecules forming a new top coating (TC) onto the primer coating P as illustrated in fig 2(II)
- 10 The main requirement for the "grafting onto" step is the presence of at least one complementary reactive group on the molecule or macromolecule to be grafted onto the precoated surface P. Therefore molecules or macromolecules to be used according to such aspect of the invention may be of various architecture obtained either by polycondensation or polyaddition reaction and bearing at least
- 15 one complementary reactive group. They may be (for instance aminopolystyrene, aminopolyimide, aminopolydimethylsiloxane, ...), proteins, enzymes, oligonucleotides, drugs, dyes, or small organic molecules of particular interest like electroactive molecules (aminoferrocene), vitamins (biotin), ligands, ...
- 20 The combination of the electrografting technique with a grafting onto process of a very wide range of molecules or macromolecules as mentioned in the third aspect of the present invention is also advantageous to increase the coating thickness and to obtain a strong adhesion of the top coating
- 25 Such approach is particularly helpful in medical applications to introduce biological polymers such as proteins which biocompatibilize and biostabilize the coated surface in its biological environment
- 30 One further advantage of all three approaches is that the coated polymer may be used to entrap or immobilize a biologically active molecule (D).
When these coatings are designed to be biocompatible and to play a biological function either intrinsically or by serving as a reservoir for biologically active

molecules, they allow said molecules to play a biological function by local
 release or contact with adjacent tissues. The polymer coating is then able to
 withstand mechanical stress and sterilization process. In the particular case of
 coronary stents, the polymer coating is able to withstand deformation such as
 5 that induced by the inflation of the balloon for optimal stent deployment.
 Particularly, said biologically active molecules are chosen for their ability to
 improve stent biocompatibility. Said active molecules might prevent, limit or
 suppress neointima formation, thrombosis or inflammatory response after stent
 implantation. Alternatively said active molecules might accelerate normal
 10 endothelial cell regeneration after stent implantation. Such agents must have
 clear antiproliferative or antithrombotic or anticoagulant or endothelial-growth-
 promoting capabilities. One such agent is a beta, alpha or gamma isotope which
 is complexed with an chelating agent and which might be incorporated into the
 proposed coating. Upon stent placement against vessel wall, said active
 15 molecules are slowly released and may interfere with the tissue reaction towards
 the metallic stent surface. The chelating agent may be hydrophilic or
 hydrophobic. Examples of chelating agents are ethylene diaminetetraacetic acid
 (EDTA), diethylene triaminepentaacetic acid (DTPA) and its analogues N-[2-
 amino-3-(rho-nitrophenyl)propyl]-trans-cyclohexane-1,2-diamine-N,N',N''-
 20 pentaacetic acid (nitro-CHX-A-DTPA) or 2-methyl-6-(rho-nitrobenzyl)-1,4,7-
 triazaheptane-N,N,N',N'',N'''-pentaacetic acid (nitro-1B4M-DTPA or nitro-MX-
 DTPA) or deferoxamine (DFO) and derivatives, hydroxyethyl starch-conjugated
 d e f e r o x a m i n e (H E S - D F O) , 4 -
 aminobenzylderivativetriethlenetetraamino hexa acetic acid (TTHA), 1,1 bis[(11-
 25 N-hydroxy)-2,5,11-triaza-1,6,10-trioxo dodecanyl] ethane (KD), ((+)-3-hydroxy-
 1-(2-hydroxyethyl)-2-hydroxyphenyl-methyl-1H-pyridin-4-one) (CGP 65015),
 sodium diethyldithiocarbamate (NaDDC), 2-(rho-nitrobenzyl)-1,4,7,10-
 tetraazacyclododecane-N',N'',N'''-tetraacetic acid (nitro-DOTA), alpha-(2-
 (rho-nitrophenyl)ethyl)-1,4,7,10-tetraazacyclododecane-1-acetic-4,7,10-
 30 tris(methylacetic) acid (nitro-PADOTA), 2-(rho-nitrobenzyl)-1,4,7,10-
 tetraazacyclotridecane-N,N',N'',N'''-tetraacetic acid (nitro-TRITA), 6,6''-

bis[[N,N,N'',N''-tetra(carboxymethyl)amino]methyl]-
4'-(3-amino-4-methoxyphenyl)-2,2':6',2''-terpyridine (TMT-amine), analogues
of pyridoxal isonicotinoyl hydrazone (PIH), desferrithiocin (DFT), cysteine, O-
phenantroline, 2-hydroxy-4-methoxypyridine-1-oxide, maltol, 1,2-Dimethyl-3-
5 hydroxypyrid-4-one, sar, diamsar, 3-cholesteryl 6-[N'-iminobis(ethylenetriolo)-
tetraacetic acid]hexyl ether (Chol-DTTA), N,N'-Bis(3,4,5-
trimethoxybenzyl)ethylenediamine-N,N'-diacetic acid, salicylaldehyde
isonicotinoylhydrazone (SIH), neocuproine, nitrilo triacetic acid (NTA), 8-
hydxyquinoline (8HQ), phosphatidylethanolamine-diethylenetriaminetetraacetic
10 acid (PE-DTTA), dipalmitoyl-phosphatidyl-ethanolamine-monomethoxy
polyethylene glycol 5000 (PE-MPEG), docosyl-triethylenetetraminepentaacetic
acid (C22TT), 1,10-phenantroline (OP). Chelating agents may also serve as
intracellular or extracellular therapeutic agent and interfere with specific
biological functions. For example, such chelator may have antioxidant properties
15 or anti-proliferative properties.

This type of encapsulation is also useful to design coatings capable of releasing
locally proteins and oligonucleotides, and in general any molecule or
macromolecule which may play a part in any biological reaction coming into
play in the physiological acceptance of the object on the surface of which the
20 polymer layer has been grafted.

Another advantage of the present invention in its three approaches is that any
miscible polymers may be blended with the coating polymer from a solution in a
solvent for both polymers by solvent casting or spin coating. Such blending is an
25 additional way to increase the coating thickness.

The following examples are illustrating the invention. The spectral conditions are the same for all examples except where otherwise mentioned.

EXAMPLE 1

- 5 **Poly(ϵ -caprolactone) coating by ring-opening polymerization of ϵ -caprolactone from Polyethylacrylate (hereafter called PEA) electrodeposited on stainless steel**

Scheme 1

- 10 The process was tested on several metallic devices like steel plate, Be[®] stent (in stainless steel 316L), and Wiktor[®] stent (in tantalum). Electropolymerization onto the metallic device was performed as follows. The metallic device was washed with heptane and acetone, and dried overnight under vacuum. Residual oxides were electrochemically reduced in acetonitrile (Aldrich)
- 15 /tetraethylammonium perchlorate (Merck) prior to use. The metallic device was immersed in a solution containing ethyl acrylate as monomer (EA, 1M, Acros), tetraethylammonium perchlorate (TEAP, 0.05 M) in dimethylformamide (DMF, Aldrich). Two platinum anodes and a platinum foil used as pseudo-reference were immersed in the solution, and the curves were recorded with an EG&G
- 20 potentiostat/galvanostat (M273A). The potential applied to the metallic device serving as a cathode was scanned down at a rate of 20 mV/s, and held constant at the value of the first reduction wave (Fig. 4, $E = -2.2$ V/Pt v. = 20mV/s, AE 1M in DMF + TEAP: a) first scan, b) second scan). It was held at this value until the current is decreased due to passivation of the metallic device, by the poly(ethyl
- 25 acrylate) coating (PEA). This passivation was confirmed by the absence of reduction during a second potential scanning. The PEA-coated metallic device was washed repeatedly with DMF and acetonitrile. The thin PEA coating having a thickness inferior to 100nm was characterized by IR-RAS spectroscopy. IR-RAS spectra were recorded by a reflexion-absorption technique (Brucker spectrophotometer) directly onto the modified electrodes whose surface reflects
- 30 light. IR-RAS spectra exhibit the $\text{C}=\text{O}$ ester band at 1739 cm^{-1} .

This first step is described in scheme 1, step 1.

The modified electrode with PEA (P in figure 1) was dried by repeated azeotropic distillation of toluene. A volume of 1 ml of diisobutyl aluminum hydride (DiBAIH) (Aldrich) in hexane ($1 \cdot 10^{-3}$ mol/l) was added dropwise to the PEA-coated metallic device immersed in toluene, and was allowed to react for 16 hours. As a result ethyl ester was transformed into aluminum alkoxide (Scheme 1, step 2), initiator of the ring opening polymerization at RT of ϵ -caprolactone (Aldrich). The reduction of ethyl ester was confirmed by IR-RAS spectroscopy. (IR-RAS spectra were recorded by a reflexion-absorption technique under air (Brucker spectrophotometer) directly onto the surface modified light-reflecting steel electrodes; the intensity of the transmitted signal being dependant on the film thickness). Since the aluminum alkoxide are unstable in the air, the reduced PEA is washed with non dried toluene which promoted the hydrolysis of alkoxide groups into alcohol for easy spectral characterization purpose. The large band at 3380 cm^{-1} is characteristic of alcohol groups which means that the alkoxide was previously formed. The band of ester carbonyl bond at 1739 cm^{-1} has decreased in intensity after a reduction time of 16 hrs, and has disappeared after 24 hrs. which underlines the bonding of the initiator.

Prior to the ring opening polymerization of ϵ -caprolactone (Aldrich), the metallic device was washed thoroughly in toluene under nitrogen in order to remove unreacted DiBAIH. It was placed in a solution of 1 ml of ϵ -caprolactone (M in figure 2) ($9 \cdot 10^{-3}$ mol) in 40 ml of toluene under stirring at room temperature (Scheme 1, step 3). Polymerization of ϵ -caprolactone was stopped after 12 hrs until 4 days by addition of an excess of HCl. The metallic device was washed extensively in toluene (Soxhlet extractor 4 days to 1 week) in order to remove the unreacted monomer and non grafted polymer if any, and then dried under vacuum. The poly(ϵ -caprolactone) coating (PCL) was confirmed by IR-RAS. The characteristic band of carbonyl groups of the PCL backbone was observed at 1728 cm^{-1} . The intensity of the signal depends on the polymerization time meaning that the polymer thickness increases with the polymerization time.

Thicknesses above some μm have been reached. The Raman spectrum also confirmed the coating of the metallic device by PCL. Raman diffusion spectroscopy was carried out with a Dilor spectrometer (SuperLabram type), equipped with a 800-2000 CCD detector cooled by liquid nitrogen and with a microscope. The spectral resolution was 2 cm^{-1} . The excitation laser beam was focused on the sample, the probed surface area being ca. $1\mu\text{m}^2$ (100X lens). Contact angles were measured by the sessile drop technique. $10\mu\text{l}$ droplets of distilled water were deposited with a microsyringe onto the polymer surface, and static contact angles were measured. All the reported data were the average of ten measurements collected from different areas of the polymer surface. It was lower on the metallic plate coated with PEA-PCL than on PEA. The measured angle (78°) onto the metallic plate coated with PEA-PCL is lower than onto PEA (92°) and higher than onto reduced PEA (56°), and was similar to the film obtained by solvent casting of PCL on stainless steel which demonstrates that PCL is completely coating the underlying reduced PEA. Peeling measurements were carried out according to the ASTM standards D3330M-90. An adhesive tape (Acrylic foam 4930, 3M) was let to adhere on the polymer coating for 24 h. It was then peeled off, and the tensile strength between the tape and the PCL film surface was measured by an Instron tensile tester. An adhesion strength higher than 1070N/m was obtained (adhesion strength of the tape onto the top-coating) and the PCL top coating remains attached onto the metallic device after peeling. In comparison, the adhesion strength values of PCL cast films from chloroform solution was 830 N/m when PCL is solvent cast onto reduced PEA electropolymerized on steel and 70 N/m when PCL is solvent cast onto PEA electropolymerized on steel. In these both cases the PCL top coating was completely removed from the surface.

EXAMPLE 2

Poly(D,L-lactide) (hereafter called PLA) coating by ring-opening polymerization of D,L-lactide from PEA electrodeposited on steel

Following the same procedure as in **EXAMPLE 1**, but replacing ϵ -caprolactone (M in figure 2) by D,L lactide, ring-opening polymerization of D,L-lactide (Aldrich, 1.3 g, 0.4 M in toluene) was initiated by the aluminum alkoxide group of PEA electrodeposited on steel and reduced by DiBAIH. Polymerization occurred at 70°C in 40 ml of toluene, and was stopped after 72 hours by addition of an excess of HCl. The PLA coating was confirmed by Raman spectroscopy with the characteristic bands appearing at 1450 and 1750cm⁻¹. Similar thickness and adhesion strength as in case of PCL(example. 1) have been obtained on these samples.

EXAMPLE 3

Poly(γ -bromo- ϵ -caprolactone) coating by ring-opening copolymerization of a mixture of γ -bromo- ϵ -caprolactone and ϵ -caprolactone from PEA electrodeposited on steel

Following the same procedure as in **EXAMPLE 1**, the ring-opening polymerization of pure γ -bromo- ϵ -caprolactone or in mixture with ϵ -caprolactone (50:50 mol/mol, 1.3 g, total concentration = 0.25, 0.5 or 0.75 M in toluene) was initiated by the aluminum alkoxide group (initiator previously called X in figs 1 & 2) of PEA electrodeposited on steel and reduced by DiBAIH. (pure γ -bromo- ϵ -caprolactone is prepared as described in M.Mazza and al in Macromolecules 2000, 33, 14)

Polymerization occurred at 70°C in 40 ml of toluene, and was stopped after a period of 72 hrs to 4 days by addition of an excess of HCl. The presence of bromine atoms in the coating was confirmed by X-ray fluorescence spectra wherein an intense signal characteristic of the K α and K β peaks of the bromine atom are clearly seen. Again, the thickness is increased up to some microns for high polymerization time (4days). Adhesion strength of the tape to the top-coating is in the range of the ones measured for pure polycaprolactone (see example1), the film being also not removed after peeling.

EXAMPLE 4

Electrografting of 1-acryloxy-2-phenyl-2-(2',2',6',6'-tetramethyl-1'-piperidinyloxy) ethane and subsequent initiation of styrene by nitroxide mediated radical polymerization (NMP)

Scheme 2

a) Electrografting of 1-acryloxy-2-phenyl-2-(2',2',6',6'-tetramethyl-1'-piperidinyloxy)ethane.

A steel or a nickel plate was immersed in a dry DMF solution of 1-acryloxy-2-phenyl-2-(2',2',6',6'-tetramethyl-1'-piperidinyloxy)ethane (monomer hereafter called ATEMPO where X is a group bearing a nitroxide type radical) The monomer is electrografted in the same experimental conditions as example 1, but ethylacrylate is replaced by the ATEMPO monomer.

Figure 5a shows the voltammogram characteristic for the electrochemical grafting of ATEMPO (1M) by scanning the potential to $E = -1.8$ V/Pt in a solution of TEAP (0.05M) in DMF, -. A decrease in the current intensity (curve b: second scan) is the signature of the electrode passivation by the formation of a polymer coating. X-ray photoelectron spectroscopy was performed on such samples (XPS was performed under ultra high vacuum (UHV), with a VG - ESCALAB 220iXL spectrometer and the monochromatised Al K α radiation at 1486.6 eV. The sensitivity factor for each element was considered for quantitative analysis. Carbon, oxygen and nitrogen atoms were detected by XPS analysis of the surface. Their atomic ratios extracted from the XPS spectrum are C/O = 7.6 and O/N = 3.75 which is in accordance with the theoretical value C/O = 6.7 and O/N = 3. Detection of signals from the underlying metallic substrate indicates that the grafted film is thinner than 10 nm.

This first step is illustrated in scheme 2, step 1

b) Initiation of styrene polymerization from the electrografted coating.

scheme 2 step 2

The steel or the nickel plate coated by poly[1-acryloxy-2-phenyl-2-(2',2',6',6'-tetramethyl-1'-piperidinyloxy)ethane] was immersed in distilled styrene (Aldrich,

10 ml) (Monomer M in figure 2) and the temperature was increased to 120°C for 24 h. Ungrafted polystyrene was removed by Soxhlet extraction with toluene for two weeks. The polystyrene coating was confirmed by Raman spectroscopy, with particularly intense bands at 1001, 1601, 3053 cm⁻¹. The molecular weight and so the thickness of the polymer coating may be controlled by addition of free alkoxyamine (benzoate of 2-phenyl-2-(2',2',6',6'-tetramethyl-1'-piperidinyloxy)ethyl up to 0.25mmol for 5ml of styrene) to the medium as illustrated in Figure 6. Indeed, the PS chains are attached to the poly[1-acryloxy-2-phenyl-2-(2',2',6',6'-tetramethyl-1'-piperidinyloxy)ethane] electrografted primer (called P in figure 2) by an ester bond, which can be hydrolyzed at high pH (NaOH 10M in THF at room temperature during 3h to 24h). It is thus possible to release PS and to have it characterized by size exclusion chromatography (SEC measurements were carried in THF at 40°C using a Hewlett-Packard 1090 liquid chromatograph equipped with a 1037A refractive index detector (columns HP PL gel 5μ (10⁵Å, 10⁴Å, 10³Å, 100Å)) and a Waters 600 liquid chromatograph equipped with a 410 refractive index detector (columns styragel HR (HR1: 100-5000, HR2: 500-20000, HR4: 5000-600000)). The columns were calibrated with PS standards). Because the probing depth of the Raman spectroscopy exceeds the thickness of the organic film, the intensity of the Raman signal is proportional to the film thickness. This expectation is confirmed by Figure 6, which shows that the intensity of the Raman signal for the aromatic units of PS at 1000 cm⁻¹ linearly changes with molecular Mass Mn of the grafted PS chains. All the experimental conditions are similar to the ones described above. Power of laser, aperture, number of scans...remain constant. When no free alkoxyamine is added to styrene, the control of the chain growth is lost meaning that the polydispersity of the chains becomes higher (above 2) but still thick films (below 5μm thickness) of adhering polystyrene are obtained.

EXAMPLE 5: Electrografting of poly(2-chloropropionate ethyl acrylate with subsequent initiation of styrene (ATRP). Scheme 3

A steel or a carbon plate was treated as example 1 but EA is replaced by 2-chloropropionate ethyl acrylate with a concentration of 0.15M (chloropropionate is X as initiator) (Fig.7, $E = -1.8$ V/Pt, in DMF + TEAP: a) first scan, b) second scan). A decrease in the current intensity was the signature of the electrode passivation by the formation of a polymer coating. The chemical composition obtained by X-ray photoelectron spectroscopy is nearly in accordance with the theoretical values (C = 58.3%, O = 28.4%, Cl = 8.3%): C = 62%, O = 31%, Cl = 7 %. Only a small amount of Cl atoms is missing due to the partial reduction of C-Cl bond during the electrografting step. This step is illustrated in scheme 3 step 1.

b) Initiation of styrene polymerization from the electrografted coating

The steel or the carbon plate coated by poly(cPEA) or by poly(cPEA-co-EA) was immersed in a solution of styrene and ATRP catalyst in toluene. For steel plates, the Grubbs catalyst ($\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$) has been used while copper catalyst with hexamethyltriethylenetetraamine (HMTETA) as ligand can be used for modification of the carbon substrates. The temperature was increased to 110°C for various period of time (4-24h). Ungrafted polystyrene was removed by Soxhlet extraction with toluene for two weeks. The polystyrene coating was confirmed by Raman spectroscopy. The molecular weight and so the thickness of the polymer coating can be control by addition of free initiator to the medium.. As for example 4, the molecular weight and so the thickness of the polymer coating may be controlled by addition of free initiator (benzyl bromide) to the medium as confirmed by Raman and SEC (Fig. 8). The thickness of the films reaches range between 1 to 5 μm without addition of free initiator. Peeling test (ASTM D3330M-90) confirmed the deposition of an adherent PS coating. The adhesion strength is above 2340N/m. PS remains on the surface after peeling. This step is illustrated in scheme 3 step 2.

EXAMPLE 6

Poly(ϵ -caprolactone) coating by electrografting of a copolymer of ϵ -caprolactone and 4-acryloyloxy- ϵ -caprolactone onto steel.

Macromolecular approach. Scheme 4.

Poly(4-acryloyloxy- ϵ -caprolactone) (poly(ACL)) and poly(4-acryloyloxy- ϵ -caprolactone-co- ϵ -caprolactone) (poly(ACL-co-CL)) are linear polyesters bearing pendant acryloyl groups along the polymer backbone called here macromonomers. Poly(ACL) with $M_n = 12000$ and $M_w/M_n = 1.25$ and poly(ACL-co-CL) with $M_n = 15000$, $M_w/M_n = 1.20$, and ACL/CL 41:59 (mol/mol) were synthesized by ring-opening polymerization with aluminum triisopropoxide as the initiator. The macromonomer is synthesised as described by X.Lou and al in Langmuir 2002, 18, 2785.

The steel device was treated as example 1 but EA is replaced by poly(ACL) or poly(ACL-co-CL) – with the concentration in acrylate groups of 1M. Electrografting has been performed by scanning the potential (v :20mV/s) to the top of the first reduction peak (E : -1.8V/Pt, Figure 9, curve a) in the bath containing the macromonomer (1M in acrylate functions in Figure 9); all the other conditions being similar to example 1. The passivation is clearly evidenced by the very low current during the second scan (Figure 9 curve b). The polymer-coated device was washed repeatedly with DMF and acetone. Contact angle of water, IR-RAS (with the bands at 2945 and 1743 cm^{-1} for alkyl and carbonyl absorption band), and peeling test (ASTM D3330M-90) confirmed the deposition of an adherent PCL coating. The adhesion strength is above 2800N/m for PACL and above 370N/m for PACL-co-CL. Scanning electron microscopy observations so as IR-RAS measurements indicated that poly(ACL-co-CL) coatings were thicker than poly(ACL) coatings which are around 350nm when prepared at high concentration.

EXAMPLE 7

Poly(ethylene glycol) network by electrografting dimethacrylate diethylene glycol (DMADEG) onto steel.

5 Macromolecular approach. Scheme 5.

In the same conditions as example 1, a steel plate was immersed in a solution containing dimethacrylate diethylene glycol (DMADEG, with a concentration =
10 0.2 to 1M, Polyscience) (here called macromonomer) rather than ethyl acrylate. The first reduction wave was already observed at a DMADEG concentration of 0.2 M. The coating formed at a concentration of 0.5M was thicker. At a concentration of 1 M, the first reduction wave was smaller, but the electrode passivation could be confirmed by the absence of reduction peak during a second
15 potential scanning. The PEG coating was confirmed by IR-RAS with the characteristic peak of the C-O bonds at 1114cm^{-1} .

EXAMPLE 8

20 Spin-coating of a poly(vinyl chloride) (PVC) top-coating onto PCL-coated steel.

Since poly(vinyl chloride) (PVC) is compatible with PCL, a THF solution of PVC was spin-coated onto poly(ACL) and poly(ACL-co-CL) coatings prepared according to **EXAMPLE 4**. The PCV top coatings was confirmed by IR-RAS with the bands at 2910 and 1721 cm^{-1} for alkyl and carbonyl groups absorptions.
25 Peeling tests (ASTM D3330M-90) showed that the PVC coating was adhering strongly to poly(ACL-co-CL) (the PVC film was not removed after peeling with an adhesion strength superior to 3700N/m) but not to poly(ACL) (the PVC film was removed by peeling with an adhesion strength of 100N/m),

30

EXAMPLE 9

Electrografting of N-acryloyloxysuccinimide with subsequent grafting of polystyrene containing primary amine groups. "Grafting onto" approach. Scheme 6.

a) Grafting of N-acryloyloxy succinimide.

Electrografting has been performed in the conditions described example 1, where ethyl acrylate has been replaced by N-acryloyloxy succinimide (concentration ranging from 0.1-3M) thus a monomer bearing a succinimidyl function as anchoring group). This monomer was prepared by reaction of 10 g of N-hydroxysuccinimide (86.9 mmol) with 7.1 ml of acryloyl chloride (86.9 mmol) in 200 ml of dried CH_2Cl_2 in presence of 12.1 ml of triethylamine (86.9 mmol). The reaction is performed overnight at room temperature with a yield after purification of 95%. The monomer structure was confirmed by RMN¹H (CDCl_3) : δ (ppm) : 2.84 (s, 4H, CH_2CH_2), 6.14 (d, 1H, $\text{CH}_2=\text{CH}$), 6.26 (q, CHCO) et 6.68 (d, 1H, $\text{CH}_2=\text{CH}$), and IR (KBr) : ν (cm^{-1}) : 3083, 3007 (C-H oléfiniques), 2955 (C-H aliphatiques), 1809-1777-1732 (C=O), 1405 (C-N) et 1213 (C-O).

According to the peeling tests (ASTM D3330M-90), the adhesion energy of the coating onto steel was higher than 3070 N/m, as compared with 1850 N/m for neat steel. The film thickness of this primer coating is low (10nm as determined by XPS) and weakly increased with increasing the monomer concentration from 0.1M up to 3M.

b) Grafting of poly[meta-(isopropyl-2-amino)styrene-co-styrene] on poly(acrylate succinimide) electrodeposited on steel

A random copolymer of styrene and meta-(isopropyl-2-amino)styrene 98.5:1.5 (mol/mol) ($M_n = 40000$) was spin-coated on the steel plate coated with poly(acrylate succinimide). The amino groups bear by the styrene backbone are complementary reactive groups that can react with X, the succinimidyl activated ester. The electrode was then heated at 150°C under vacuum for 24 h. Unreacted

polystyrene was removed by Soxhlet extraction in THF for 2 weeks. The FTIR-RAS spectrum of the modified electrode confirmed the deposition of polystyrene (bands at 3086, 3064, 3028, 2927 and 1601, 1487, 1444 and 1001 cm^{-1} typical for styrene unit). Moreover, the grafted polystyrene film was not detached by the peeling test (ASTM D3330M-90).

c) Grafting of ferrocene amine on poly(acrylate succinimide) electrodeposited on steel

Ferrocene amine was grafted onto the polyacrylate succinimide (P in Figure 1) by the grafting onto technique (Figure 2 b). For this purpose, the modified carbon or gold plates were immersed during 6 days at room temperature in 5ml of a DMF solution containing 0.1 g of aminoferrocene (synthesized following Van Leusen D. et al, *Organometallics*, 2001, 20, 224-226.) and a catalytic amount of dimethylaminopyridine. After rinsing in DMF and acetonitrile, the binding of the ferrocene to the surface has been evidenced by cyclic voltammetry (Figure 10) which shows the electroactivity of the ferrocene in the anodic potential range for various scanning rates (100, 50 and 20 mV/s).

d) Grafting of biotine-cadaverine on poly(acrylate succinimide) electrodeposited on steel

Biotine-cadaverine (Aldrich) was grafted onto the polyacrylate succinimide (P in Figure 1) by the grafting onto technique (Figure 2 b). For this purpose, the modified platinum, gold or ITO-glass (see below) plates with grafted polyacrylate succinimide were immersed during 4 days at room temperature in 12.5 mg of biotine-cadaverine (N-(5-aminopentyl)biotinamide) (MM 442.50 $n=2,83.10^{-5}$ mol) and 2.85 mg of triethylamine (MM 101.19 $n=2,83.10^{-5}$ mol) and catalytic amount of dimethylaminopyridine dissolved in 2.5 ml of dried DMF. After reaction, the substrate is rinsed in DMF and acetonitrile. The efficient binding of the biotine-cadaverine to the device was evidenced by colorimetric

t e s t u s i n g dimethylaminocinnamaldehyde
(following Vanwetswinkel S., et al., *Bioorganic & Medicinal Chemistry*, 1995, 3
(7), 907-915.). Figure 11 shows the absorbance of the coating revealed by the
dye (curve a) in comparison without the dye (curve b). This spectrum was
5 recorded by UV-VIS spectrophotometer (Hitachi U3300) using electrografted
transparent substrates consisting of glass coated with a thin conducting layer of
indium-tin oxide (ITO-glass).

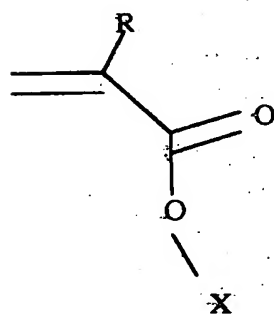
EXAMPLE 10

10 **Incorporation of a fluorescent molecule, rhodamine-6G, within a PCL film
casted on a grafted PEA-PCL coating, and release in aqueous medium**

PCL was grafted from a PEA primer coating electrografted onto steel (20 x 10 x
1 mm-plate), as described in **EXAMPLE 1**. Three ml of a solution of PCL (10
15 wt%, $M_n=5.8 \cdot 10^3$) and rhodamine-6G (11.2 wt%, 336 μ g) in chloroform was cast
onto the PEA-PCL coated plates, followed by a chloroform solution of PCL
alone to cover the previous PCL with Rhodamine top-coating. The plates were
then immersed into 1 ml of phosphate buffer (0.13 M, pH 7.4) at 37°C. The
whole aqueous volume was collected at regular times and replaced with fresh
20 buffer. The concentration of rhodamine-6G in the aliquots was determined by
fluorescence spectrometry (excitation wavelength 526 nm, emission wavelength
550 nm). At the end of the release study (6.75 days), the PCL top coating was no
longer adhering and had detached from the surface. However, low-angle IR
spectroscopy revealed that the surface remained covered with PCL, probably
25 coming from the electrografted PEA-PCL coating. Rhodamine-6G was released
regularly from the PCL coating, with a limited burst effect at early times more
likely due to the PCL top coating (Fig. 12).

CLAIMS:

1. Process for depositing by electro-grafting a strong adherent polymer coating onto an electrically conductive surface comprising an electrochemical grafting at the surface of an active monomer for forming a primer coating P onto said surface and having as general formula:



wherein R represents hydrogen or methyl and characterised in that the monomer comprises an X group which is part of a preformed polymer or is as an intermediate agent for polyaddition reaction or is an anchoring group for attachment of a molecule having at least one complementary reactive group

2. Process according to claim 1 wherein X is an intermediate agent of polyaddition .
3. Process according to claim 2 wherein the intermediate agent is an initiator for radical polymerisation via nitroxyde radical(NMP) reacting with a second monomer for forming a polymer top-coating TC.

4. Process according to claim 3 wherein the initiator is an alkoxyamine for the initiation of styrene polymerisation

5

5. Process according to claim 4 wherein the monomer is 1-acryloxy-2phenyl-2(2', 2', 6', 6'-tetramethyl-1'piperidinyloxy)ethane.

10

6. Process according to claim 2 wherein the intermediate agent is an initiator for radical polymerisation via atom transfer polymerisation(ATRP) reacting with a second monomer for forming a polymer top coating TC.

15

7. Process according to claim 6 wherein the monomer is (2-chloropropionate of ethyl acrylate for forming poly(2-chloropropionate) ethyl acrylate as primer coating P.

20

8. Process according to claim 6 to 7 further comprising a metallic complex to catalyse the atom transfer polymerisation for forming a polymer top coating TC.

25

9. Process according to claim 8 wherein the polymer top coating is polyester.

30

10. Process according to claim 2 wherein the intermediate agent is an initiator or a transfert agent for reversible-addition-fragmentation (RAFT) for forming a polymer top coating TC.

- 5 11. Process according to claim 1 wherein the intermediate agent is an initiator for ring opening polymerisation(ROP) reacting with a second monomer for forming a polymer top coating TC.
12. Process according to claim 11 wherein X is an alkoxide preferably an aluminum alkoxide.
- 10 13. Process according to claim 12 wherein the monomer is ethyl acrylate.
14. Process according to claim 13 wherein the second monomer is ϵ -caprolactone for forming poly(ϵ -caprolactone) as polymer top coating.
- 15 15. Process according to claim 12 wherein the second monomer is D,L-lactide for forming poly(D,L-lactide as polymer top coating.
16. Process according to claim 1 wherein X is part of a preformed polymer.
- 20 17. Process according to claim 16 wherein the preformed polymer is biocompatible and/or biodegradable.
18. Process according to claim 17 wherein the preformed polymer is (homopoly(4-(acryloyloxy)- ϵ -caprolactone)(polyACL),
- 25 19. Process according to claim 14 wherein the preformed polymer is polyethyleneoxide diacrylate .

20. Process according to claim 1 wherein the X is an anchoring group for attachment of a molecule or a macromolecule having at least one complementary reactive group.

5

21. Process according to claim 20 for the attachment of a macromolecule forming a polymer top coating.

10

22. Process according to claim 20 to 21 wherein the complementary reactive group is an amino group.

23. Process according to claim 20 to 22 wherein X is N-acryloyloxy succinimide.

15

24. Process according to claim 23 wherein the macromolecule is polystyrene containing amino groups.

25. Process according to claim 24 wherein the top coating is poly(meta-(isopropyl-2-amino)styrene-co-styrene)

20

26. Polymer coating on an electrically conductive surface obtained by the process according to claim 1 to 25.

25

27. Polymer coating according to claim 26 having an adhesion strength superior to 3700 N/m.

28. Polymer coating according to claim 26 having a thickness superior to one micron.

30

29. Use of the polymer coating obtained by the process according to claim 1 to 25 for a metallic prosthesis.

30. Use according to claim 29 for a stent.

5 31. Use of the polymer coating obtained by the process according to claim 1 to 25 as barrier coatings.

32. Use of the polymer coating obtained by the process according to claim 1 to 25 as insulating layers.

10 33. Use of the polymer coating obtained by the process according to claim 1 to 25 as anti-scratching.

15

Figure 1

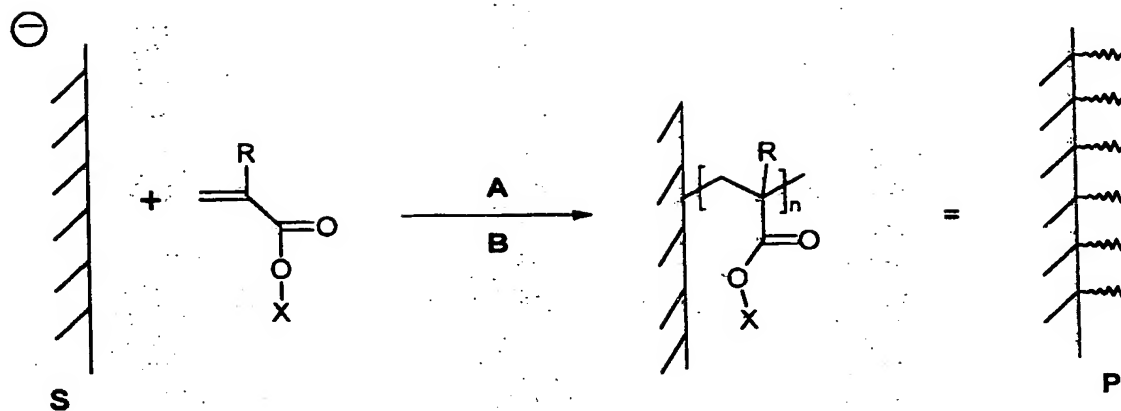


Figure 2

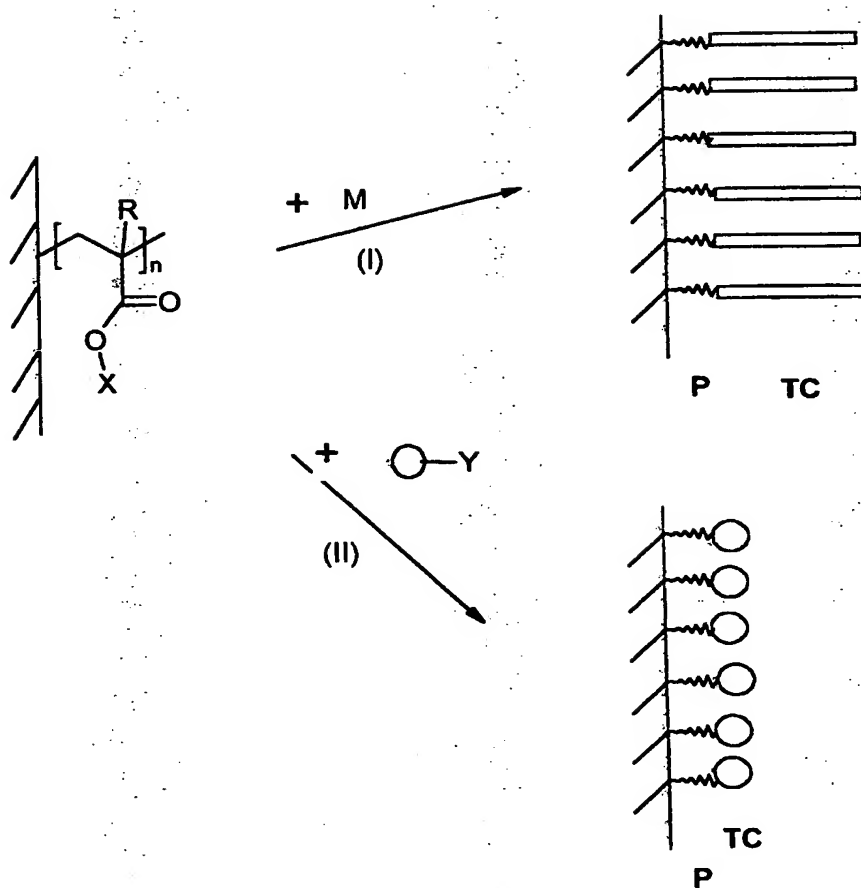


Figure 3

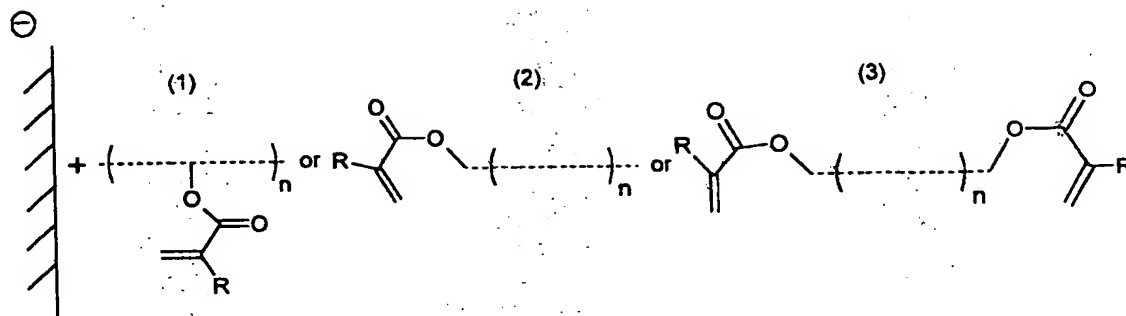
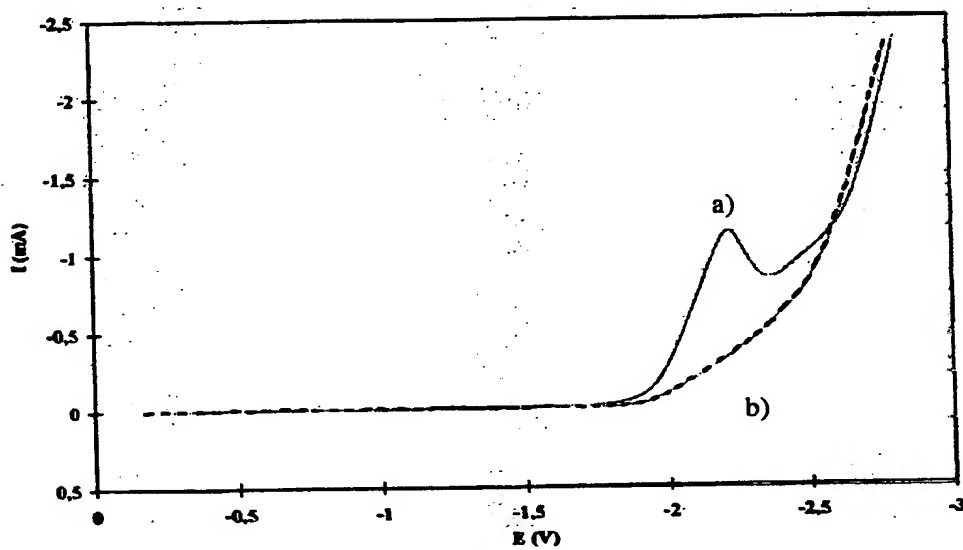


Figure 4



3/10

Figure 5

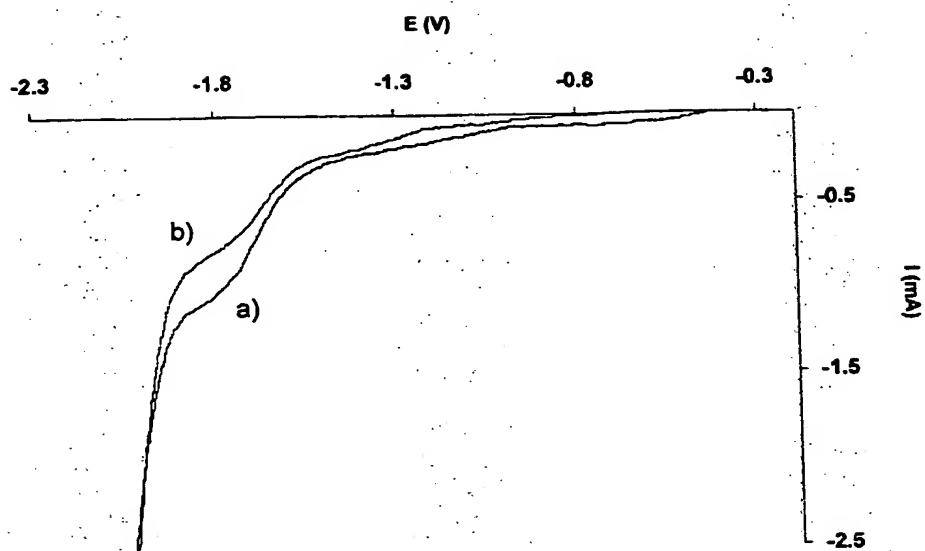
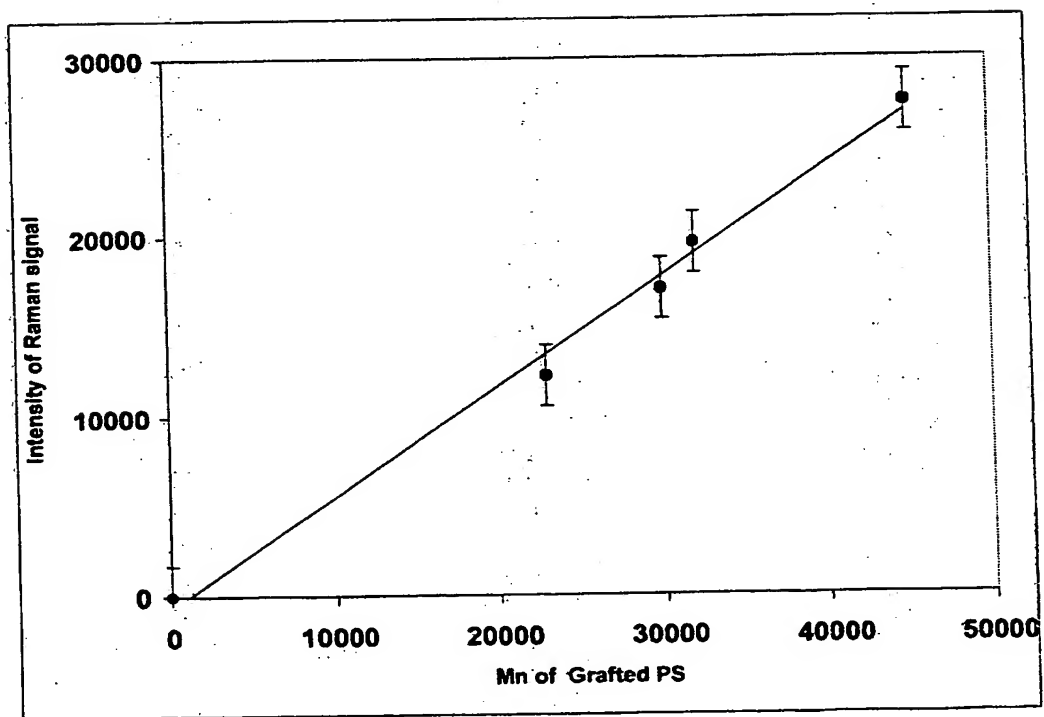


Figure 6



4/10

Figure 7

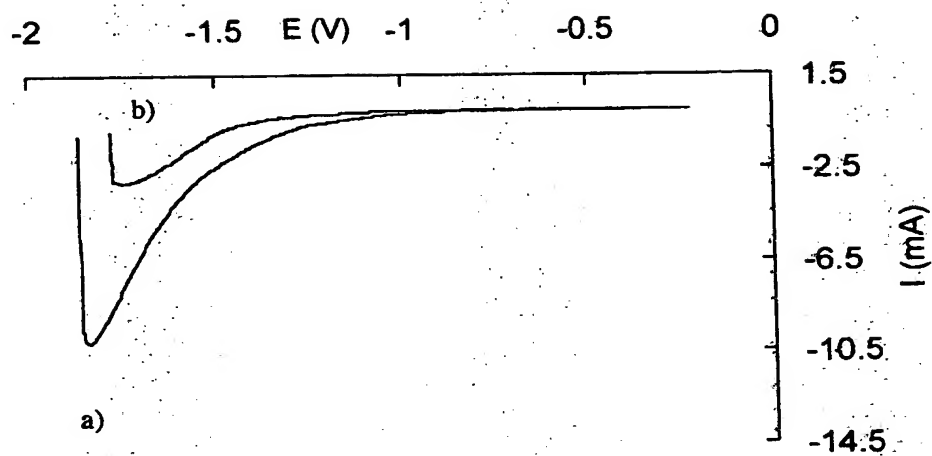
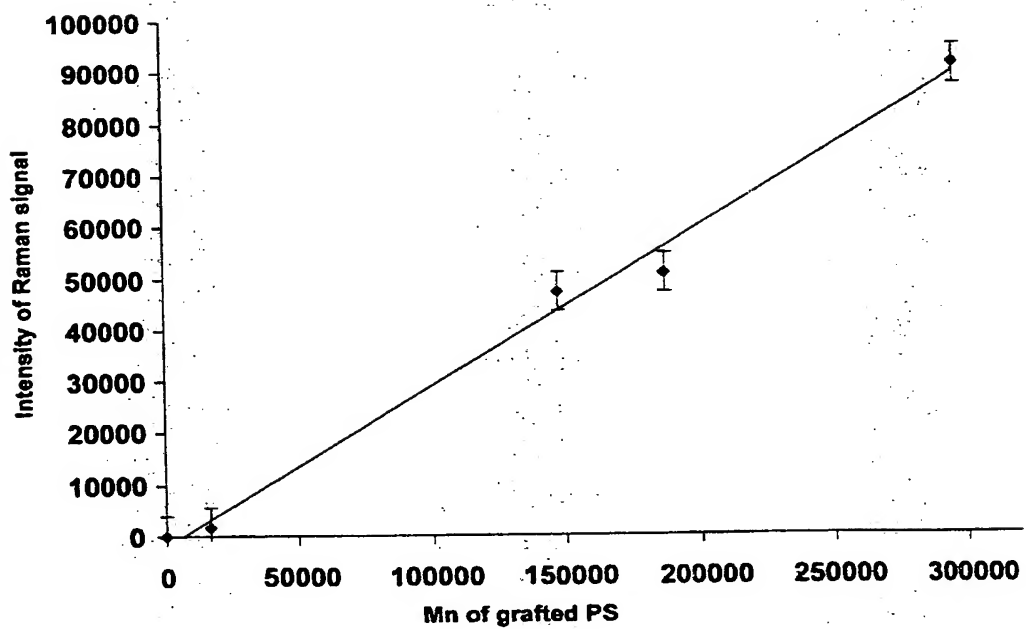


Figure 8



5/10

Figure 9

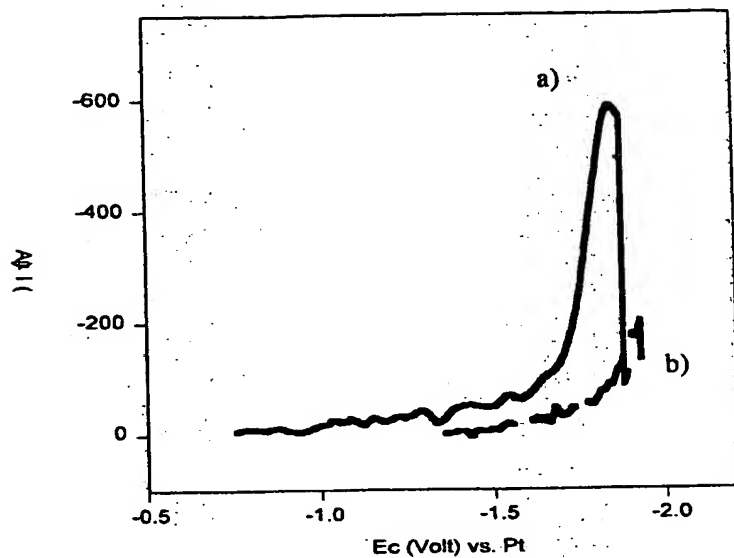
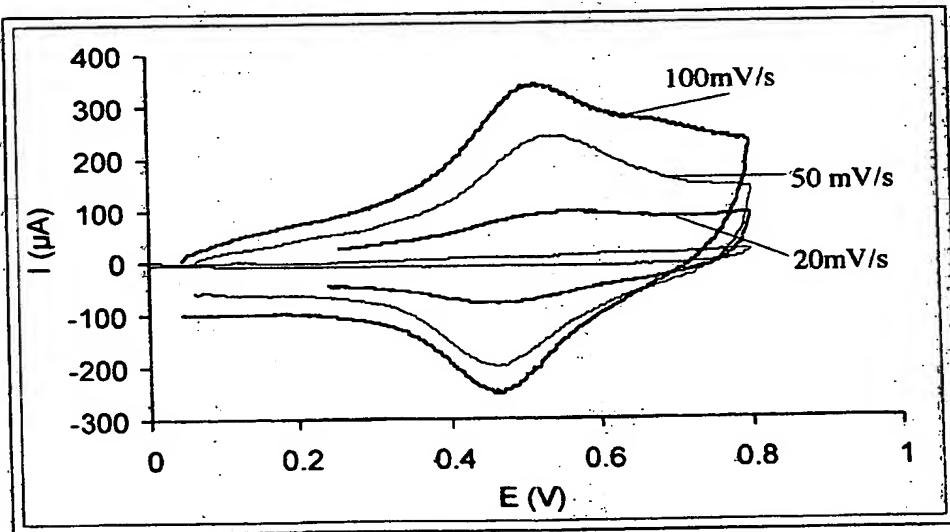


Figure 10



6/10

Figure 11

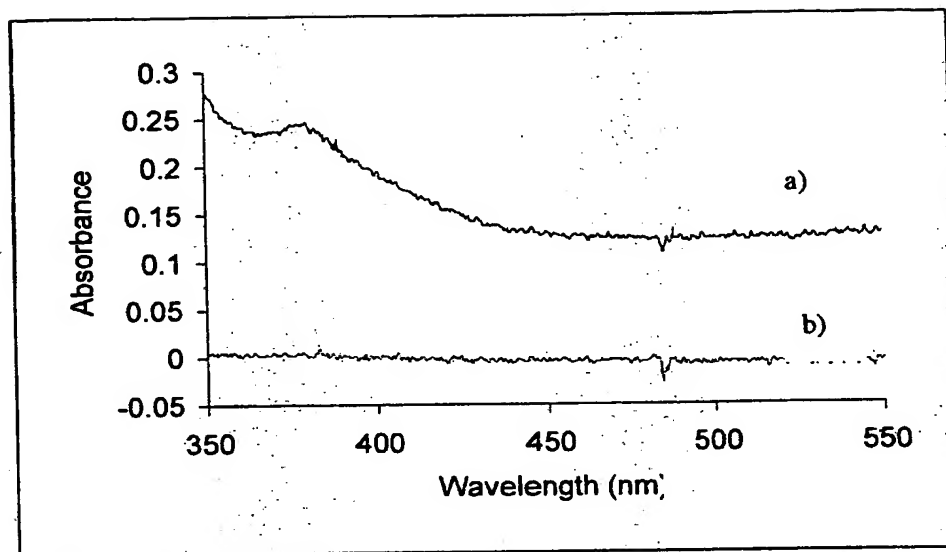
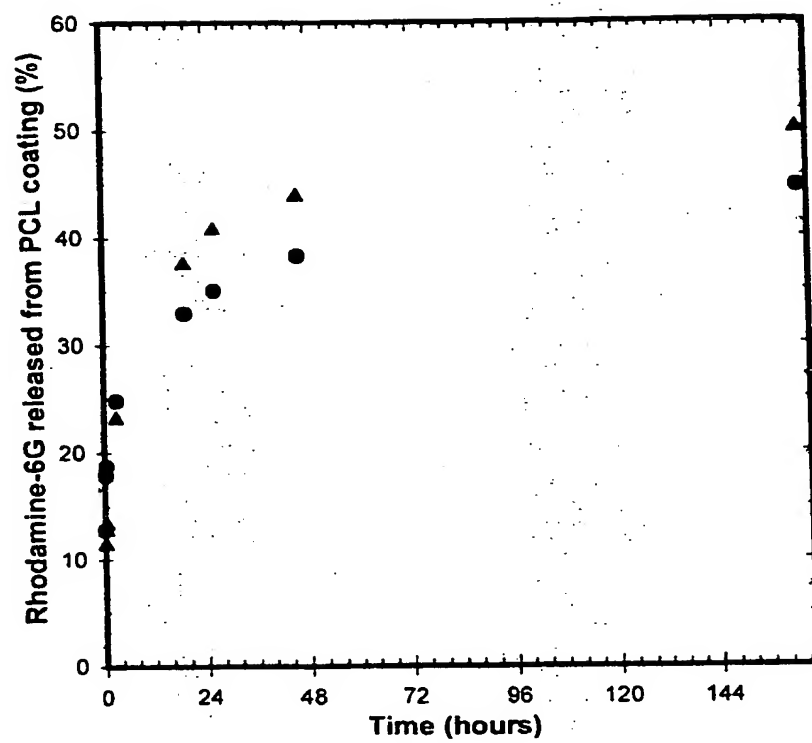
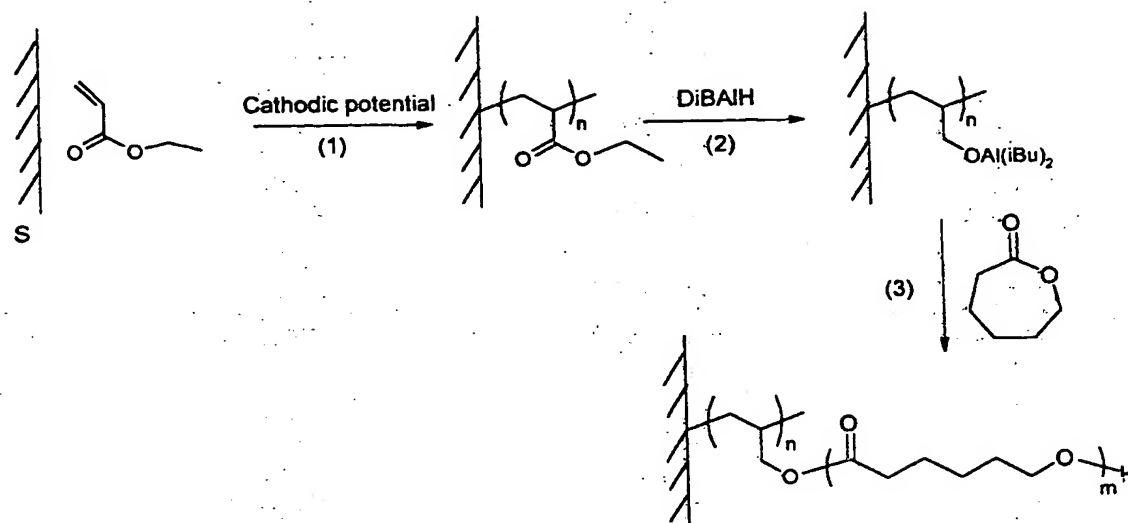


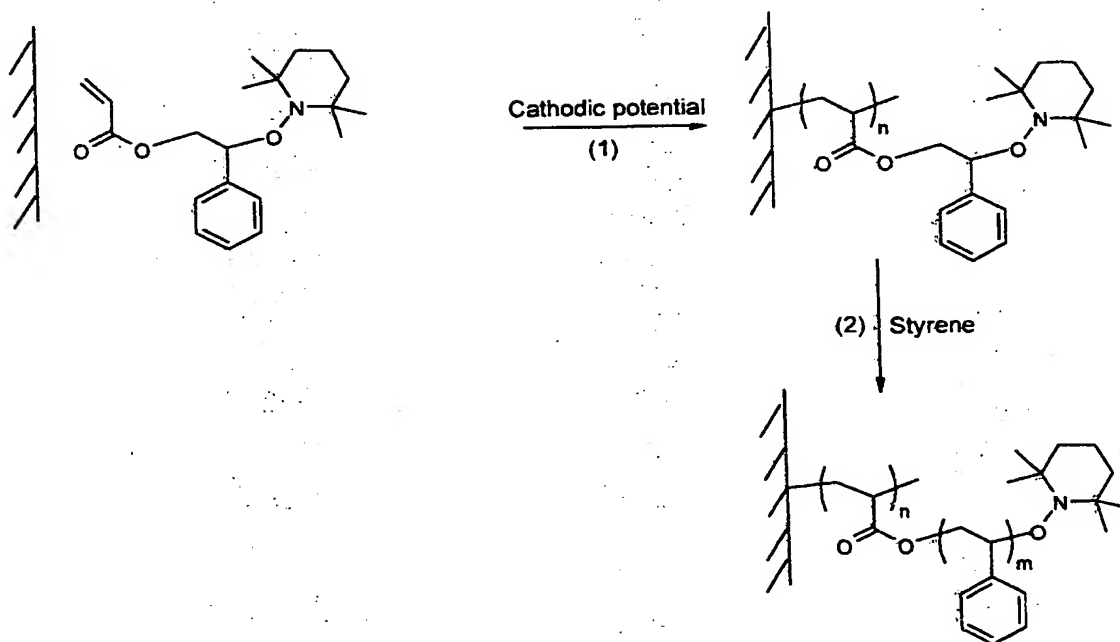
Figure 12



Scheme 1

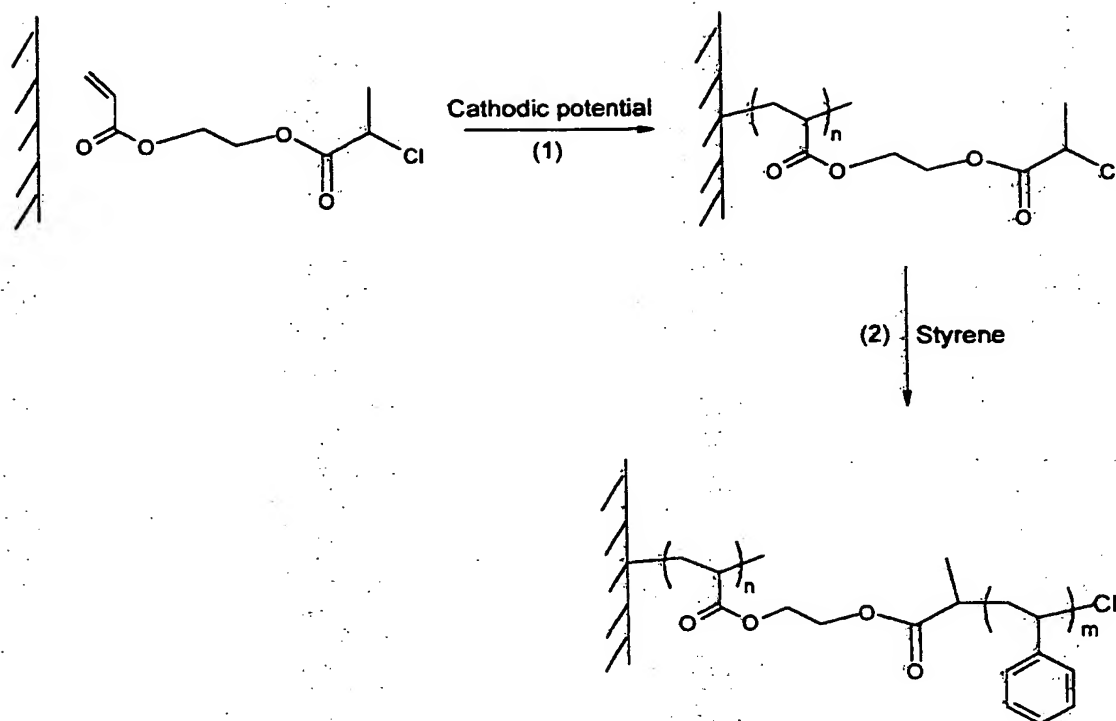


Scheme 2

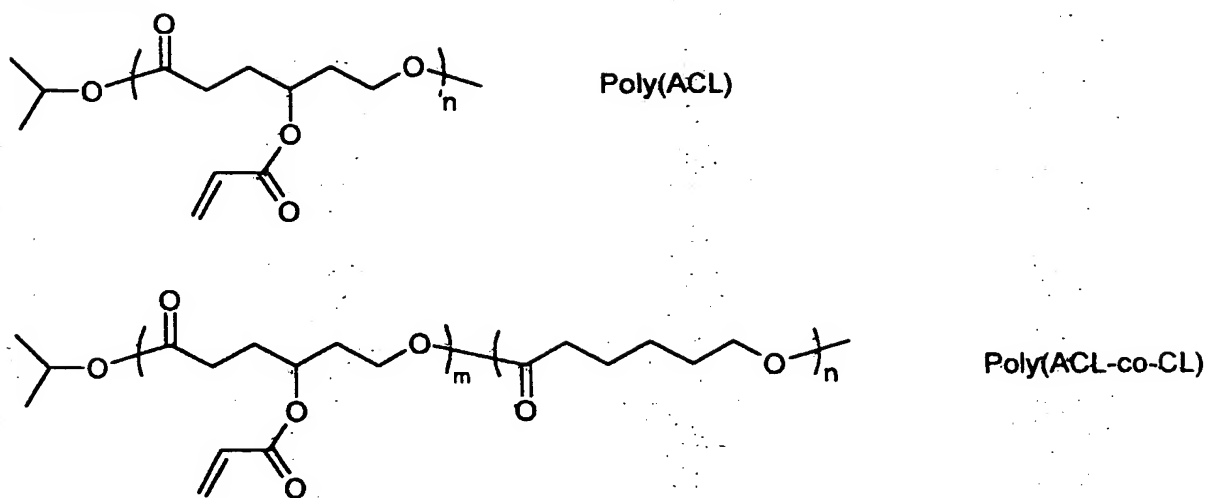


9/10

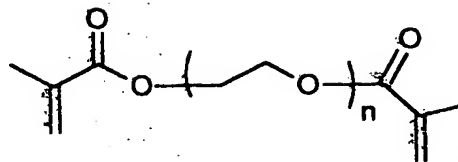
Scheme 3



Scheme 4

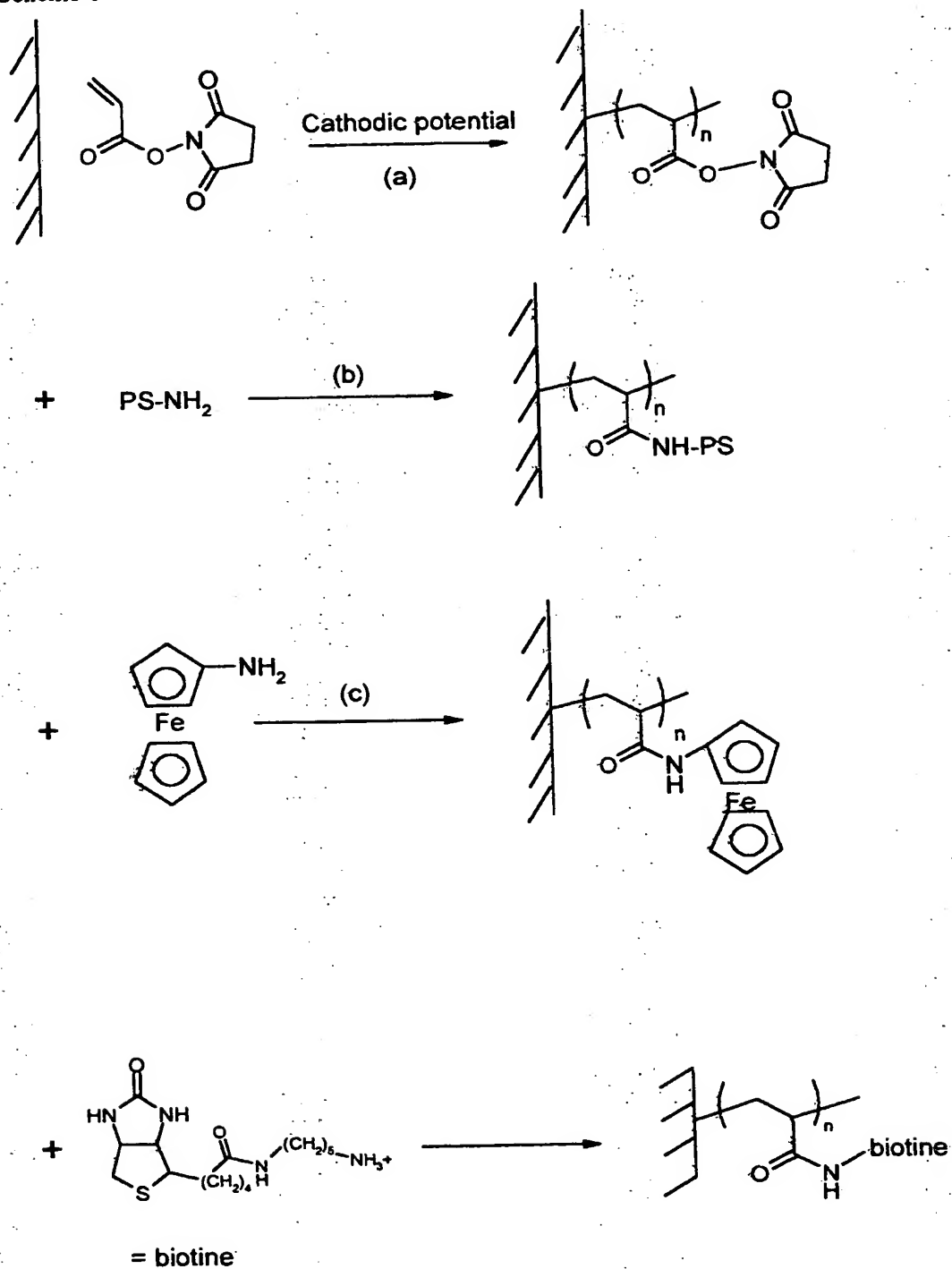


Scheme 5



10/10

Scheme 6



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 December 2002 (12.12.2002)

PCT

(10) International Publication Number
WO 02/098926 A3

(51) International Patent Classification⁷: C08F 8/00,
2/58, 292/00, C09D 5/44

(21) International Application Number: PCT/EP02/06433

(22) International Filing Date: 3 June 2002 (03.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/297,714 4 June 2001 (04.06.2001) US

(71) Applicant (for all designated States except US): UNIVER-
SITE DE LIEGE [BE/BE]; Interface Entreprises Univer-
sité, Antheunis Nicole, Quai Van Beneden, 25, B-4020
Liege (BE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BERTRAND,
Olivier [BE/CA]; Chemin St-Louis; 2590, Sainte-Foy,
Québec G1W1N2 (CA). JEROME, Robert [BE/BE]; Rue
Alexandre Beaupain, 4, B-4845 SART-JALHAY (BE).
GAUTIER, Sandrine [BE/BE]; rue Bois-l'Evêque, 132,
B-4000 Liege (BE). MAQUET, Véronique [BE/BE];
Hameau de Crenwick, 19, B-4257 Berloz (BE). DE-
TREMBLEUR, Christophe [BE/DE]; Wolfskaul, 5,
51061 Köln (DE). JEROME, Christine [BE/BE]; rue
de la Jacinthe, 10, B-4102 Ougree (BE). VOCCIA,
Samuel [BE/BE]; rue Saint Michel, 46, B-4000 Liege
(BE). CLAES, Michael [BE/BE]; Rue Ernest Malvoz,
49, B-4020 Liege (BE). LOU, Xudong [CN/BE]; Place
général Leman, 41, B-4000 Liege (BE). LABAYE,
David-Emmanuel [BE/BE]; Rue Hubert Désamuré, 29,
B-4000 Liege (BE).

(74) Common Representative: UNIVERSITE DE LIEGE;
Interface Entreprises Université, Antheunis Nicole, Quai
Van Beneden, 25, B-4020 Liege (BE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES,
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,
MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG,
UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS,
MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI,
CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for all designations

Published:

- with international search report

(88) Date of publication of the international search report:
16 October 2003

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 02/098926 A3 (54) Title: PROCESS FOR DEPOSITING STRONG ADHEREND POLYMER COATING ONTO AN ELECTRICALLY CON-
DUCTIVE SURFACE

(57) Abstract: Process for depositing by electrografting a strong adherent polymer coating onto an electrically conductive surface comprising an electrochemical grafting at the surface of an active monomer for forming a primer coating P onto said surface and having as general formula: X0 (meth)acrylate wherein X is either part of a preformed polymer or is an intermediate agent for polyad-
dition reaction or is an anchoring group for attachment of a molecule having at least one complementary reactive group. Such process allows formation of new primer by one-step electro-grafting of a reactive polymer called macromonomer. Such process also allows further modification of an initial electrografted polymer (called primer-coating) to increase the coating thickness by the so-called grafting-from technique i.e. polymerization of a second monomer or to introduce other types of polymers (also called top-coating) via covalent attachment between the primer and the top coating through the X ester group by the so called grafting onto technique. Such process also allows to graft onto the primer coating compounds like functional polymer, peptide, protein, oligonucleotide, dyes, drugs, anti-bacterian compounds.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/06433

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08F8/00 C08F2/58 C08F292/00 C09D5/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C08F C09D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 38 06 014 A (LICENTIA GMBH) 7 September 1989 (1989-09-07) page 2, line 48 -page 3, line 3 claims 1-3,13	1,26,28
A	CH 623 608 A (BATTELLE MEMORIAL INSTITUTE) 15 June 1981 (1981-06-15) examples claims 1,2,6	1,26,28
A	PATENT ABSTRACTS OF JAPAN , 20 September 1994 (1994-09-20) & JP 06 166954 A (OSAKA GAS CO. LTD.), 14 June 1994 (1994-06-14) abstract see also Derwent abstract AN 1994-230840 --- -/-	1,26

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

23 May 2003

Date of mailing of the international search report

06.06.2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bettels, B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/06433

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 102, no. 12, 1985 Columbus, Ohio, US; abstract no. 102 150938, SHAPOVAL, G. S.; PUD, A. A.; BAGRII, V. A.: "Modification of a steel surface by electrochemical polymerization" XP002221569 & Neftepererabotka i Neftekhimiya (Kiev) (1984), 27, 45-8 abstract	1,19,26, 28
X,P	LOU X ET AL: "Electrografting of Preformed Aliphatic Polyesters onto Metallic Surfaces" LANGMUIR, ACS, WASHINGTON, DC, US, vol. 18, 3 January 2002 (2002-01-03), pages 2785-2788, XP002223305 ISSN: 0743-7463 see entire paper	1,2,9, 14,15, 17,26,28
A	TAKEUCHI Y ET AL: "PREPARATION OF AMPHIPHILIC CARBON BLACK BY POSTGRAFTING OF POLYETHYLENIMINE TO GRAFTED POLYMER CHAINS ON THE SURFACE" POLYMER BULLETIN, SPRINGER VERLAG, HEIDELBERG, DE, vol. 41, no. 1, 1 July 1998 (1998-07-01), pages 85-90, XP000771787 ISSN: 0170-0839 see entire paper	1,2,16, 21,22
A	WO 98 12530 A (SOANE BIOSCIENCES INC) 26 March 1998 (1998-03-26) claims 1,2,9,10	1,20,21, 26
A	GB 1 348 819 A (TOYOTA MOTOR CO LTD) 27 March 1974 (1974-03-27) page 1, line 44 - line 65 examples 6,10-13 claims 1,3,9	1,13,26
A	BAUTE N ET AL: "BONDING ELECTROPOLYMERIZATION: A NEW ELECTRON-TRANSFER STRATEGY FOR THE TAILORING OF PERFORMANT POLYMER-BASED COMPOSITES" MACROMOLECULAR SYMPOSIA, WILEY VCH, WEINHEIM, DE, vol. 134, October 1998 (1998-10), pages 157-166, XP000801475 ISSN: 1022-1360 see entire paper	1

-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/06433

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	REINHARD G ET AL: "SCHICHTBILDENDE ELEKTROPOLYMERISATION VON ACRYLSÄURE UND KORROSIONSSCHUTZ" FARBE + LACK, CURT R. VINCENTZ VERLAG. HANNOVER, DE, vol. 96, no. 12, 1 December 1990 (1990-12-01), pages 942-946, XP000216568 ISSN: 0014-7699 see entire paper	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/06433

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 (in part), 16-19, 26-33 (in part)

Process for the preparation of a polymer coating on an electrically conductive surface by electro grafting, comprising electrochemical grafting of a reactant containing a (meth)acryloyl structural element, characterised by (i) the (meth)acryloyl group being part of an oligomer.

2. Claims: 1 (in part), 2-15, 26-33

Process for the preparation of a polymer coating on an electrically conductive surface by electro grafting, comprising electrochemical grafting of a reactant containing a (meth)acryloyl structural element, characterised by (ii) the (meth)acryloyl group being part of an intermediate product which can initiate (further) polyaddition reactions.

3. Claims: 1 (in part), 20-25, 26-33 (in part)

Process for the preparation of a polymer coating on an electrically conductive surface by electro grafting, comprising electrochemical grafting of a reactant containing a (meth)acryloyl structural element, characterised by (iii) the (meth)acryloyl group being part of an anchoring group.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/06433

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
DE 3806014	A	07-09-1989	DE 3806014 A1	07-09-1989
CH 623608	A	15-06-1981	CH 623608 A5	15-06-1981
JP 06166954	A	14-06-1994	NONE	
WO 9812530	A	26-03-1998	US 5935401 A	10-08-1999
			AU 4431597 A	14-04-1998
			EP 0927352 A2	07-07-1999
			JP 2001500971 T	23-01-2001
			US 2002053399 A1	09-05-2002
			WO 9812530 A2	26-03-1998
			US 6176962 B1	23-01-2001
			US 6056860 A	02-05-2000
GB 1348819	A	27-03-1974	JP 49023808 B	18-06-1974
			CA 945109 A1	09-04-1974
			DE 2162284 A1	06-07-1972
			US 3759797 A	18-09-1973